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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,421	CLERICI ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-4, 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/15/2010 has been entered.

2. The amendment to the specification mailed 01/15/2010 has been entered.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

3. Claims 1, 3-4, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the determining the existence of predisposition or diagnosis of Alzheimer's disease by determining the allelic variant of G to A at -1082 of IL-10 in a human. The claims are limited to additionally analyzing to determine the presence of -174C allele in IL-6 and ApoE4 carrier status. The claims are further limited to additionally analyzing to determine the presence of -1082A allele for IL-1. Newly added claim is drawn to a method for the determining the existence of predisposition or diagnosis of Alzheimer's disease by determining the allelic variant of G to A at -1082 of IL-10 , -174C allele in IL-6 and ApoE4 carrier status in a subject.

The nature of the claims requires knowledge of a correlation between detection of the presence of a -1082A allele of IL-10, -174C allele of IL-6, -1082A allele of IL-1, the status of ApoE4 carrier and diagnosis and predisposition to Alzheimer's disease (AD). The nature of the claims requires that the presences of the alleles are both indicative of risk as well as having AD.

Newly added claim 21 encompasses analysis of any subject, including human and non-human.

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification teaches the present invention is related to a process of whether IL-10 and IL-6 SNPs were related with the development of AD (pg 3, 2nd last para.). The specification teaches that AD is a clinical syndrome characterized by complex and heterogeneous pathogenic mechanisms (see pg. 1, last para). The specification teaches that the allele e4 of ApoE significantly increases the risk of AD but it is neither necessary nor sufficient for the development of the disease (See pg. 2, 1st paragraph).

The specification asserts that the combination of IL-10 and IL-6 has been found to be more strongly predictive of predisposition to Alzheimer's disease (see pg. 9, 2nd para.). The specification further teaches that ApoE has been associated with sporadic and non-sporadic Alzheimer's and hence a further aspect is the polymorphic allele of IL-10, IL-6, and Apo-E (see pg. 9, 3rd para). The specification further asserts the presence or absence of additional allelic variations of cytokines, specifically IL-10, IL-6, Apo-E and IL-1 (see pg. 9, 5th para.)

The specification demonstrates a working example (example 1) of 47 AD patients and 25 non-demented subjects (see pg. 13, last para). The specification demonstrated whole blood samples were taken and genotyped for IL-10 (see pg. 14). The specification demonstrates genotyping for the promoter region of IL-10 and performing statistical analysis (See pg. 15). The specification teaches that different IL-10 genotypes among AD patients was significantly skewed as shown in table II. However table II demonstration the relation to age of AD onset and

table I demonstrates the frequency of different genotypes of AD patients to healthy controls (table I, table II and pg. 16, 1st full para). The specification asserts that the frequency of different genotypes among AD patients was statistically different from health controls and gives a p value of .007, however the specification does not provide any guidance with what the p value represents, its unclear if its the comparison of all alleles of AD to healthy control or specific individual allele of AD to healthy control (see pg. 4, last para). The specification asserts that the presence of the ATA/ATA and GGC/ATA genotypes were associated with earlier age at disease onset with a p value of . 042 demonstrated in table II and the inverse correlation was detected for low IL-10 producing genotypes, table III.

The specification demonstrates a working example of 65 AD patients and 65 health controls (See pg. 22, example 2). The specification teaches obtaining blood samples from the individuals and genotyping the samples for IL-10 and IL-6 as well as ApoE genotype (See pg. 23). The specification teaches that the genotype and allele frequencies of the bialleleic polymorphism at position -1082 is reported in table V (see pg. 24). The specification asserts that AD patients who a significantly higher frequency of -1082A which skews the genotype distribution in AD compared to healthy controls (see pg. 24). Table V demonstrates that the A allele is statistically significant in the population of AD patients analyzed however it unclear how the distribution of the allele and p values were determined. According to table V, there were 63 AD patients analyzed, however the text of the specification teaches that 65 patients were analyzed. (see pg. 25 and pg. 23). The specification asserts that table VI shows the distribution of IL-6 with AD and healthy control patients. According to table VI, the allele is statistically significant however table VI demonstrates a total of 59 AD patients, 50 with C allele and 68 with

G allele but the specification teach that 65 patients were analyzed (see pg. 26 and pg. 23). Table VII of the specification demonstrates the IL-10 and IL-6 allele risk for AD however the A allele of IL-10 and the C allele of IL-6 has a p value greater than .05 (see pg. 27). It is unclear that in one association study 63 patients were studied and another association 59 patients were studied.

The specification does not teach the analysis of IL-1 or ApoE4 carrier in AD patients.

The specification does not teach predictably associating the -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with diagnosis or predisposition to AD in any human. The specification does not teach predictably associating -1082A of IL-10, -174C of Il-6, ApoE4 carrier allele with diagnosis or predisposition to AD in any subject, human or non human.

It is noted that the claims are drawn to both determining risk as well as determining the presence (diagnosis) of AD. The specification does not demonstrate a predictable assay to determine diagnosis of AD nor provide a predictably assay to distinguish between diagnosis versus risk. The specification does not demonstrate taking an unknown population and correctly classifying the individuals as having AD. Furthermore, the specification does not teach how to predictably determine that the presence of the allele will determine either diagnosis or risk. For example, if a skilled artisan would determine the presence of -1082A allele of IL-10 in a human subject the specification does not provide guidance on how to determine if this person has AD or is just at risk of developing AD.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does teaches is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable as larger genotyping studies of different ethnicities of AD patients did not find a predictable correlation between -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 alone or in combination with diagnosis or predisposition to AD in any human or non-human animal.

Furthermore, the post filing art is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable. The prior art analyzes several different populations and larger sample sizes and found that each of the alleles -1082A of IL-10, -174C of Il-6, or -1082A IL-1 is not predictably correlative to diagnosis or predisposition to AD.

The post filing art teaches that -1082A is not associated with AD in different populations. For example, Bagnoli et al. (Neuroscience Letters (207 418:262-265) teaches that there have been conflicting results of IL-10 polymorphisms and their association with AD (See abstract). Bagnoli et al. teach that three studies in Italian and Chinese populations demonstrate that -1082A allele of Il-10 is significantly over represented in AD patients however there are other studies that have not been able to replicate these results and that the role of IL-10 gene in AD may be limited to certain populations (See pg. 262, last para.). Bagnoli et al. analyzed -1082A of 222 AD patients and 179 normal controls (see pg. 263, 1st column, 1st para.). Bagnoli et al. teach

many authors have investigated the role of -1082A allele as genetic risk factor for AD with conflicting results. Bagnoli et al. teach a study of 132 AD patients from northern Italy found the -1082A allele was increased in AD patients, in contract a study of 406 German AD patients and 215 Italian AD patients did not replicate these findings, and finally another paper of an American population found no statistical significance in the case-control groups (see pg. 264, 1st column, last para.) Bagnoli et al. teach that no overexpression of the -1082A allele or distribution was found in AD patients, which confirm two Italian studies and a Chinese case-control study (See pg. 264, 1st column, last para.) Therefore, Bagnoli et al. demonstrate the unpredictability of association -1082A allele with AD in a small population study, such as that taught in the instant specification.

Additional post filing art teaches the unpredictability of association -174C allele of IL-6 with AD. Capurso et al. (Exp. Gerontology, 2004, vol. 39, pp. 1567-1573) teach a genotyping study of AD patients in northern and southern Europe (see abstract). Capuroso et al. teach multiple studies have been conducted to determine the association of -174G/C allele with AD (see table 1). Capurso et al. teach that the association between IL6 -174 G/C promoter polymorphism and increased risk of AD has been evaluated in four ethnic groups with contrasting findings (See pg. 1568, 1st column, 1st para.) Capurso et al. teach analysis of 388 subjects from southern Italy with 168 AD patients (See pg. 1568, 2nd column, last para.). Capurso et al. teach no evidence of an association of IL-6 -174 G/C promoter polymorphism with AD. Capurso et al. teach a study with larger sample size did not show an association with IL-6 -174 G/C promoter polymorphism and risk for AD (see pg. 1571, 2nd column, last para). Capuros et al. teaches the explanation of the conflicting results is unclear but that perhaps there

is linkage disequilibrium with another biological relevant locus on chromosome 7 or the polymorphism is due to non-random association with a functional mutation on the gene (see pg. 1572, 1st column, 1st full para) Capurso et al. teaches that a large meta-analysis of genetic association studies with common diseases indicate that only a third to a half of all associations ultimately prove to be significant, emphasizing the importance of larger samples (See pg. 1572, 1st column, 1st full para).

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to

complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong.

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$

should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Pepe (Am J Epidemiology, 2004, 159:882-890) demonstrates the necessary statistically analysis to effectively classify a person according to their current or future diagnostic, prognostic, or screening outcome. Pepe teaches that if a marker identifies 10% of controls as positive (false positive) and the odds ratio is 3 then it will correctly identify only 25% of cases as true positive. Pepe demonstrates that even an odds ratio of 16 will fail to detect over 40% of cases (See figure 2 and pg. 884). Pepe demonstrates that even strong statistical associations between outcome and marker do not necessarily imply that a marker can discriminate between persons likely to have outcome and those who do not (see pg. 882). Pepe demonstrates that markers proposed for classifying or predicting risk in individual subjects must be held to a much higher standard than merely being associated with outcome and teaches that their sensitivities and specificities must be shown to be adequate through appropriate statistical evaluations. Pepe demonstrates the unpredictably of classifying an individual based on the presence of a marker, particularly based on the odds ratio of the SNP marker presented in the instant application (OR of 3.0 and 5.8 for IL-6 and IL-10).

The Alzheimer Research Forum contains a database that comprises meta-analysis of all published polymorphisms associated with AD. The met-analysis demonstrates that the odds ratio of the polymorphism rs1800896, -1082G/A of IL-10 has an odds ratio of between .8-1.1m which as demonstrated by Pepe will not accurately classify an individual. Furthermore the data presented demonstrated the unpredictably of association this allele with AD as some of the studies were not included due to negative results (see alzgene), The meta-analysis demonstrates that replication studies of polymorphism rs1800795, -174G/C of IL-6 could be not be performed because four independent case-control samples was not eligible for inclusion.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate with the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD, as the specification does not teach a large sample size, analyze different ethnic groups or provide confidence levels greater than 95% for the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination. The specification only teaches a subject population of 65 AD patients with statistically significant data for the analysis of an association between -1082A IL-10 and AD patients however the number of patients in the table (Table V) is not consistent with the sample population and further the post filing art demonstrates that in a larger sample size in different ethnicities was demonstrated not to be predictably correlative to AD. Thus the prior art demonstrated the unpredictably of determining a human subjects risk or diagnosis of AD based on the presence of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to the association the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD to determine if in fact there was either an association between the polymorphism an individuals and AD. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not the following alleles -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1, alone or in combination would be responsible for determining the predisposition or diagnosis to AD in any human. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to AD. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

4. The response traverses the rejection pages 5-15 of the remarks mailed 09/04/2009. The response asserts that IL-10 and IL-6C alleles are associated with AD. The response asserts that applicants have determined that impaired IL-10 response to the presence of ßamyloid is a feature of AD and impaired IL-10 response is implicated in production of ßamyloid. The

response asserts that applicant's data suggest that a subject inability to product IL-10 in response to ßamyloid is likely to aid ßamyloid accumulation and contribute to AD. The response asserts that the data in the specification clearly demonstrate that elevated levels of IL-10 prevent occurrence of AD or ameliorate progression of disease. This response has been thoroughly reviewed but not found persuasive. The claims are not drawn to method of determining levels of IL-10, preventing occurrence of AD, or ameliorating progression of disease. The claims are drawn to both diagnosis and predisposition of AD by genotyping a subject, which as stated above is not enabled by the instant specification.

The response asserts that 65 AD patients and 65 healthy patients were used for genotyping. It is noted that analysis in table V and VI is not on 65 AD but 63 and 59 patients, respectively. In response to the office action mailed 01/17/2008, the response addresses the incorrect table references in the specification and states that 6 patients could not be reliably typed due to insufficient number of cells. However, it is noted, as stated in the paragraph above even with the correction of the table references in specification, this does not address why 63 were examined for IL-10. Its unclear how 6 patients could not be typed for IL-6 but not for Il-10. Regardless of the inconsistency in the table versus text of the specification with regard to the number of AD patients assayed (59, 63, or 65) correction for this population would not change the enablement issues of the instant claimed invention as the specification only provides for a small population and the post filing art is replete with evidence that the association of these two polymorphisms with AD is unpredictable in many different populations. The response asserts that there is no reason to doubt the objective truth of any of the statements made in the specification as there is nothing within the specification to indicate that the data and analysis

presented are inconsistent or unreliable. This response has been thoroughly reviewed but not found persuasive. It is the totality of the evidence in the prior art with regard to the association of -1082 of IL-10 and -174 of IL-6 that gives reasons for the uncertainty of the enablement because the evidence provided by the examiner provides support that the specification fails to teach how to make and use the association of -1082 of IL-10 and -174 of IL-6 with AD in any population without undue experimentation. As stated in MPEP, 2164.05(a), if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered, In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). Thus the evidence provided by the examiner demonstrates that the association of -1082 IL-10 as well as -174 of IL-6 with AD was not possible even in a much larger population after the filing date of the application. Additionally the specification does not provide guidance to determine if an individual will have AD or is only at risk of having AD based on the presence of the same polymorphism. For example, if the -1082 A allele was determined in a subject would this subject have AD or just at risk of AD? The specification provides no guidance on how to determine or classify a subject as risk versus having AD.

The response asserts that although Bagnoli and Capruso purportedly differ from the findings described by Applicants. The response assert that Bagnoli and Capruso do not provide teaching that would invalidate Applicants finding and thus Bagnoli and Capruso fail to provide reasonable objective truth of the statements contained within the specification. The response asserts that Bagnoli and Capruso acknowledge that their results may not be definitive or conclusive. The response asserts that the main finding of Bagnoli and Capruso is not that their

data necessarily contradicts with previous studies but that other explanations could account for the observed differences. The response asserts that different countries may have different clinical criteria for diagnosing AD and difference in criteria could result in some variation. The response asserts that an important aspect of the study of the instant application was exclusion of patients with inflammation and that without performing the study of Bagnoli and Capruso according to Applicant's experimental design it is not possible to exclude any contribution to these affects. This response has been thoroughly reviewed but not found persuasive. The claims are drawn to diagnosis and risk of AD in any human patient and any subject, human or non-human. The claims are not limited to a population of patients that do not have inflammation, therefore the study of Bagnoli and Capruso is relevant. Furthermore, assertion that different criteria in different countries could account for the variation in the study is not found persuasive. Bagnoli and Capruso as well as Ma, Cambarros, and Infante, cited by applicant, teach that the association of IL-10 -1082 A allele with AD is not reliably applicable to any population and demonstrate that further studies on larger and different populations controlling for ethnic and geographic variability needs to be conducted, thus demonstrating that it is not the criteria of different countries but the ethnic and geographic variability of the association of IL-10 -1082 allele with AD that accounts for the unpredictability. The specification does not provide any teaching or guidance to determine which group of individuals having the -1082 A allele of Il-10 will be associated AD based on ethnic or geographic status. Furthermore the meta-analysis study by alzgene.org demonstrates the unreliability of IL-10 at -1082 and IL-6 at -174 being associated with AD. The specification does not teach or provide any guidance to determine which population will be predictive and which population will not be predictive of having AD based on

the genotype of IL-10 at -1082 thus based on the guidance in the specification along with the preponderance of evidence post filing that the association is not predictive, the method of determining a diagnosis or predisposition to AD based on the genotypes claimed in any subject or any human is unpredictable and required undue experimentation.

The response asserts that certain patients that have -1082 IL-10 are at an increased risk of developing AD and that use of IL-1082 IL-10 with other AD markers is likely to be useful in assessing a subject's AD risk. The response asserts that the claimed subject matter is fully enabled whether or not the marker is useful for predicting AD risk in every subject. This response has been thoroughly reviewed but not found persuasive. The specification does not provide any guidance in which "certain" patients the IL-10 -1082 is diagnostic. The examiner is not asserting that every population needs to be associated with risk however the specification must provide guidance without undue experimentation as to which population would be enabled and which population would not be enabled. Based on the evidence in the art in it would be undue experimentation based on the guidance in the specification which "certain" patients would be associated with risk or having AD based on the IL-10 -1082 genotype.

The response asserts that there is literature that confirms the study upon which the present application is based and cites Combarros et al, Ma et al, and Infante et al. However, Combarros et al. teaches that only heterozygosity of IL-10 at -1082A allele was associated with a small increase of AD risk (see pg. 864, 2nd column, last para and table 1). Additionally, Combarros et al. teaches that their study does not allow for rigorous analysis of gender specific differences in AD risk association and additional studies using different sets of patients and controls are required to confirm the effect, thus Combarros et al. does not confirm what is present in the

specification as Combarros et al. teaches that there is only a small effect seen with only the heterozygous -1082 A allele and teaches that more studies are necessary. Ma et al. teach that genotypic distribution in the AD group did not differ significantly from the control group for the IL-10 -1082 polymorphism (see pg. 1007, 2nd para, 1st full para). Mat et al. teach that there are ethnic differences between populations that may account for the different associations with the disease (see pg. 1009, 1st column, last para). Ma et al. does not teach a predicative association of any allele of -1082 with risk of AD (See table 2). Thus Ma does not provide evidence that the study upon which the instant invention is based is predictive and infact teaches the unpredictability of association the -1082 allele with AD in different ethnic populations (see pg. 1009, 1st column, last para and pg. 1005, 2nd column, last para). Infante et al. teach a study of Caucasian subjects and teach that C/C genotype of IL-6 is related to decrease risk of AD and the A/A genotype of -1082 of IL-10 was not associated with AD (see pg. 1135, 2nd column, 1st full para). Infante et al. teach the interaction effect of both polymorphisms did have an effect on lower risk of developing AD. Thus, Infante et al. does not demonstrate the finding in the specification, as Infante et al. demonstrate that homozygous A at position -1082 of IL-10 along with homozygous C at position -174 of IL-6 is associated only with a decreased risk but -1082 alone is not predictive. It is noted that the claims are drawn to any risk, thus the claims encompass both an increase and decreased risk and claim 1 is drawn to both homozygous and heterozygous A of -1082 of IL-10 in any population. Thus neither Combarros, Ma, or Infante provide evidence that the claimed invention of any risk in any population of human, having either a homozygous or heterozygous -1082 of IL-10 is enable and in fact each of the reference

provide further evidence of the unpredictability of associating the polymorphism with Alzheimer's disease.

The response asserts that none of the references teach controlling for inflammation and examining amyloid specific immune response and thus the references cited by the examiner fail to support the enablement rejection of the claims. This response has been thoroughly reviewed but not found persuasive. The claims are not limited to a population of patients that are without inflammation or are the claims drawn to examining amyloid specific immune response. The claims are drawn to determining a predisposition or diagnosis of AD in any subject or any human by the presence of a polymorphism at position -1082 of IL-10. The art cited by the examiner demonstrates the unpredictability of associating -1082 allele of IL-10 with AD.

The response asserts that making and using the invention is not unpredictable and that additional studies using a larger sample size would confirm the results of the Applicants study. The response asserts that conducting analysis of 168 subjects is not unduly burdensome. The reasons assert that the specification provides considerable direction and guidance on how to screen for AD. It is noted that the examiner is not asserting that genotyping subjects is unduly burdensome, the examiner is asserting that based on the evidence in the art the predictably of -1082A of IL-10 with AD is highly unpredictable thus the skilled artisan in order to perform the claimed method would have to determine which population would associated with increased risk of AD and which population would be associated with having AD based on the presence of -1082A allele IL-10 which is highly unpredictable and thus would require undue experimentation undergoing many different genotyping assaying in many different populations to predictably determine the association of -1082A allele of IL-10 with increase or decrease risk of AD or

diagnosis of AD. The instant specification, although providing guidance on how to genotype subjects does not provide any guidance on how to determine which population would be predictably associated with risk of AD versus having AD nor provide any guidance on how to determine which population is predictably associated with AD as the art demonstrated the unpredictably of reproducing the association of -1082 of IL-10 in different populations.

As evidence in the art, the association of -1082A of IL-10 with increase or decrease risk of AD or diagnosis of AD in any ethnic population is unpredictable thus claimed invention is not enabled.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

5. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Sarae Bausch/
Primary Examiner, Art Unit 1634